

#### THE. USE OF CHARTIE CONTROLINES FOR THE INHIBITION OF FLK-1 MEDIATED VASCULOGENESIS AND ANGIOGENESIS



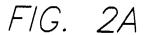
Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

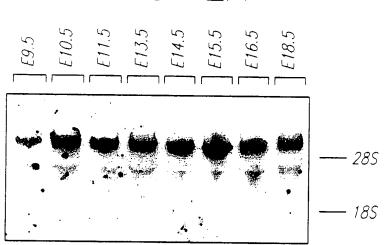
## FIG. 1

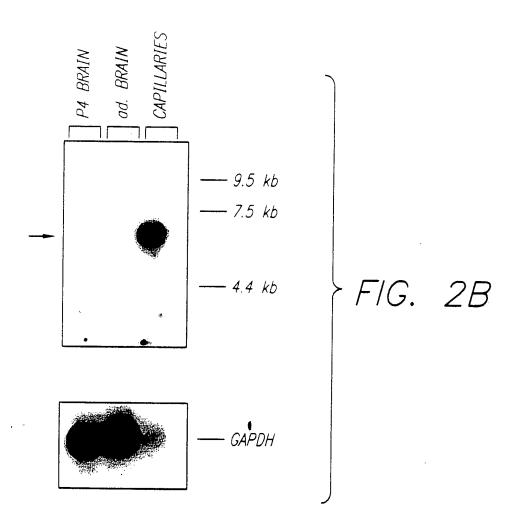
FLK-1 KDR TKR-C	ILIHIGHHLNVVNLLGACTKPGGPLMVIVEFSKFGNLSTYLRGKRNEFVPYKSKGARFRO        S        S
	GKDYVGELSVDLKRRLDSITSSQSSASSGFVEEKSLSDVEEEEASEELYKDFLTLEHLIC
FLK-1 KDR TKR-C	YSFQVAKGMEFLASRKCIHRDLAARNILLSEKNVVKICDFGLARDIYKDPDYVRKGDARL

#### FOR THE INHIBITION OF FLK-1 MEDIATED VASCULOGENESIS AND ANGIOGENESIS

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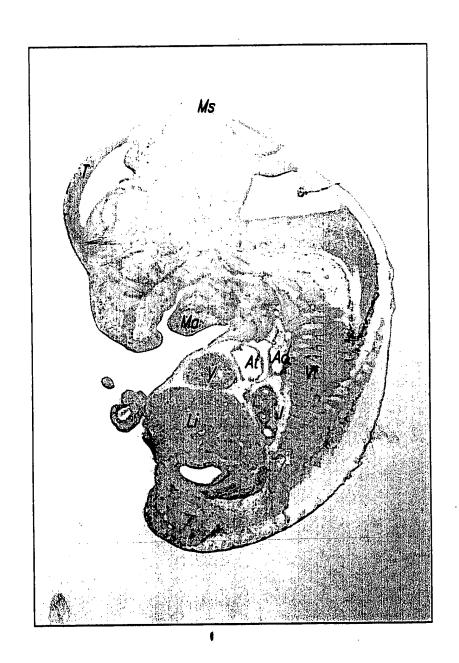






# MEDIATED VASCULOGENESIS AND ANGIOGENESIS Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

FIG. 3A



## MEDIATED VASCULOGENESIS AND ANGIOGENESIS

Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

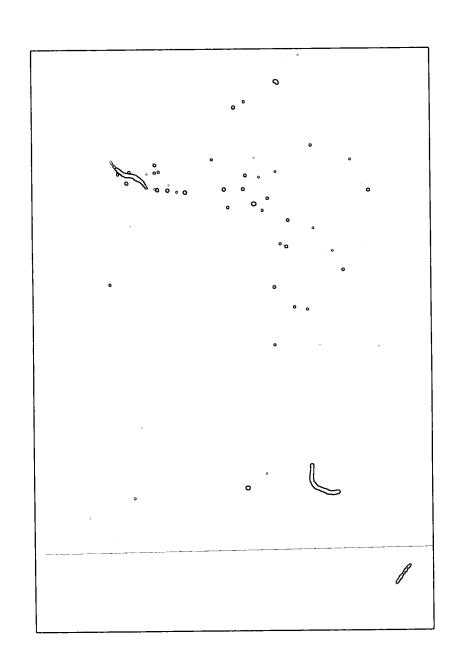
FIG. 3B



## MEDIATED VASCULOGENESIS AND ANGIOGENESIS

Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

FIG. 3C

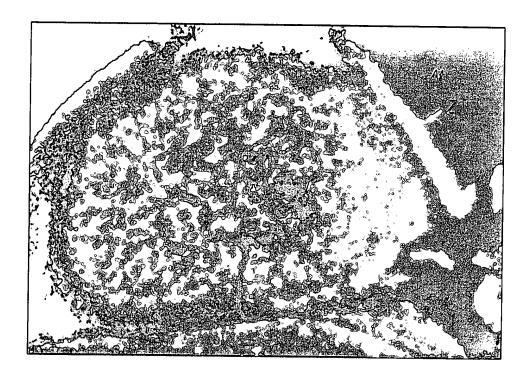


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ANGIOGENESIS
Inventor(s): Axel ULLRICH et al.

FIG. 4A



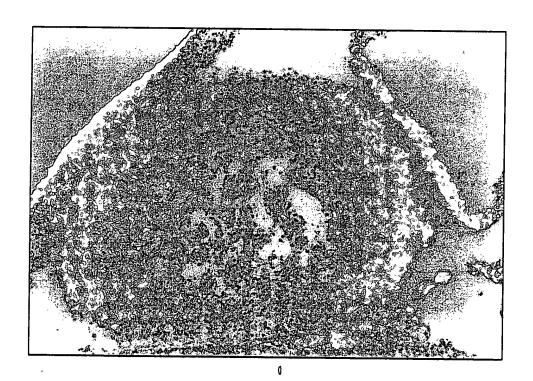
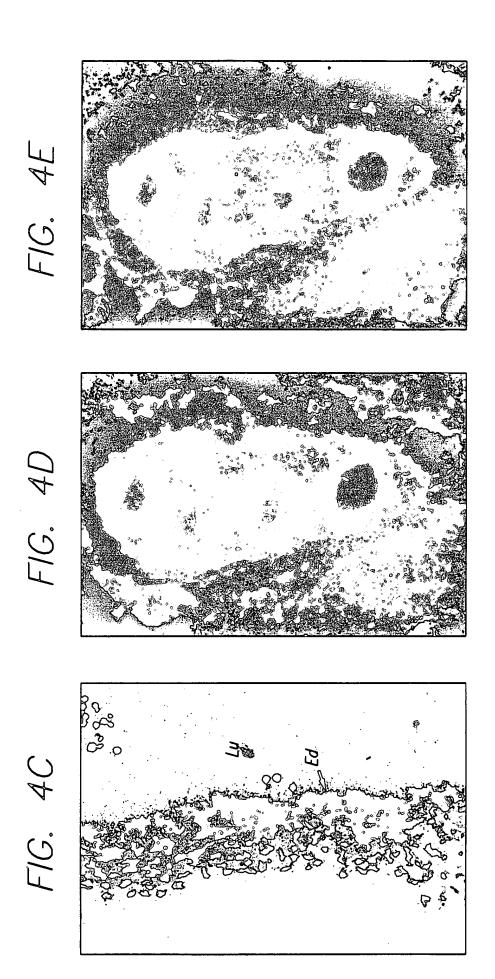


FIG. 4B

## MEDIATED VASCIII OGENESIS AND ANGIOGENESIS

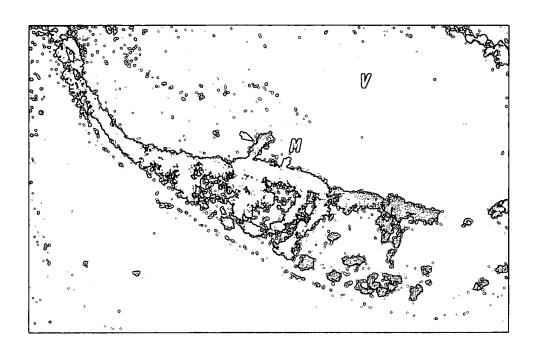
Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678



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Appl. No.: 09/766,678

FIG. 5A



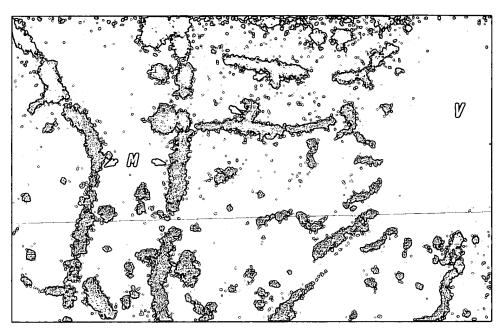
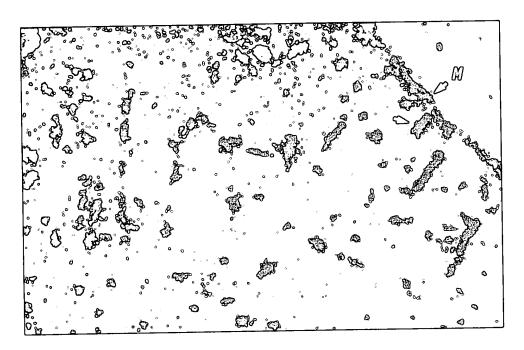


FIG. 5B

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FIG. 5C



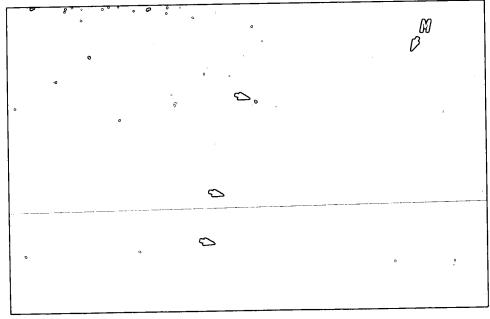
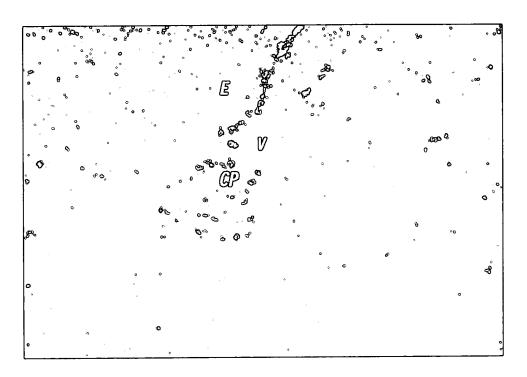


FIG. 5D

## WEDIATED VASCULUGENESIS AND F. /

Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

FIG. 6A



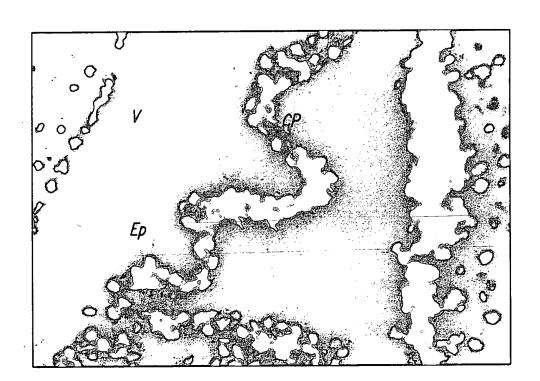
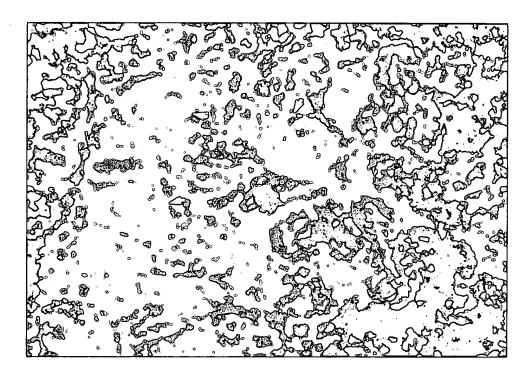


FIG. 6B

FIG. 7A



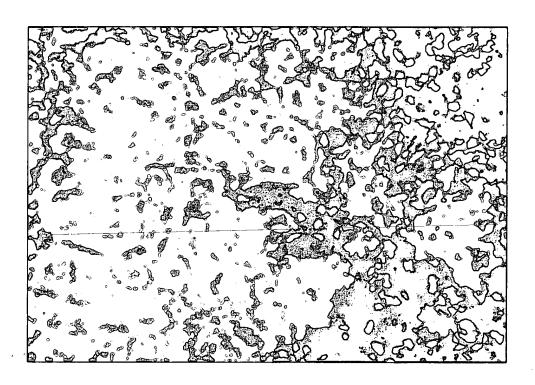
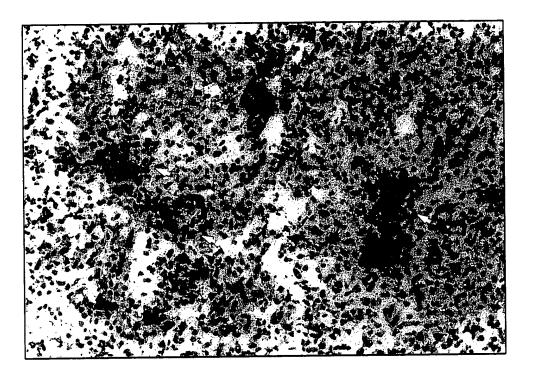


FIG. 7B

## MEDIA LED YAM JIH AMBENESIS AND 3 3 ANGIOGENESIS Inventor(s): Axel ULLRICH et al.

FIG. 7C



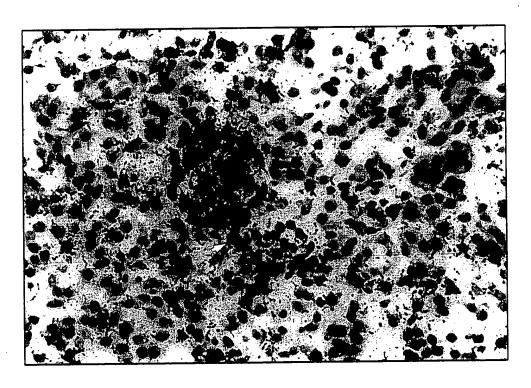


FIG. 7D

### MEDIATED VASCIILOGENESIS AND ANGIOGENESIS

Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

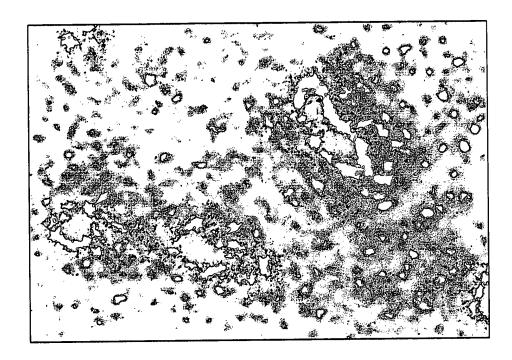
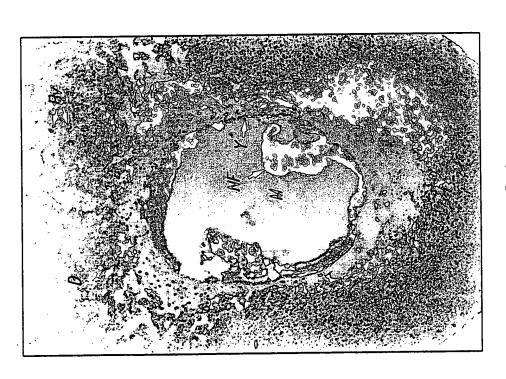


FIG. 8B



F1G. 84

## MEDIATED VASCULOGENESIS AND ANGIOGENESIS

Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

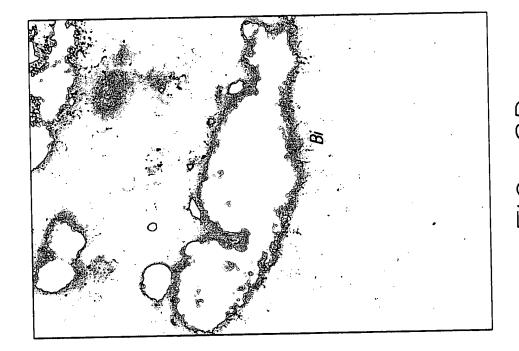
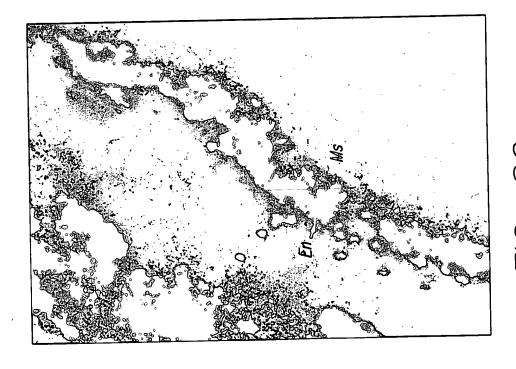
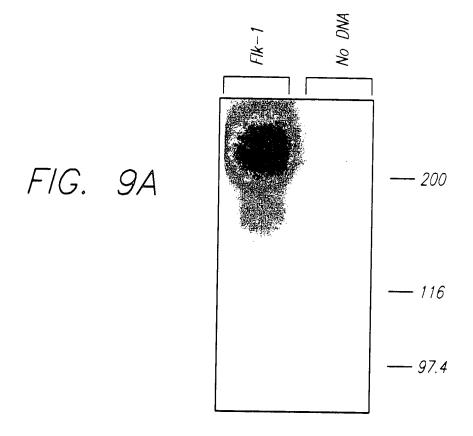


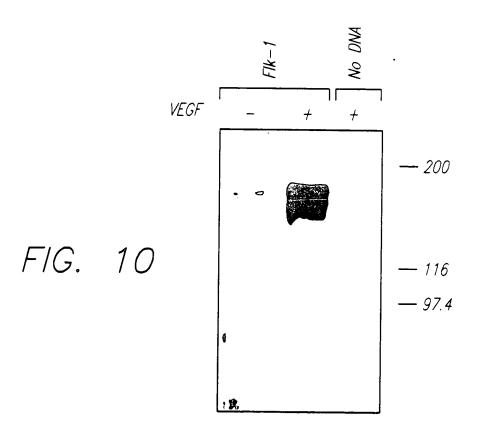
FIG. 8D



Ω.

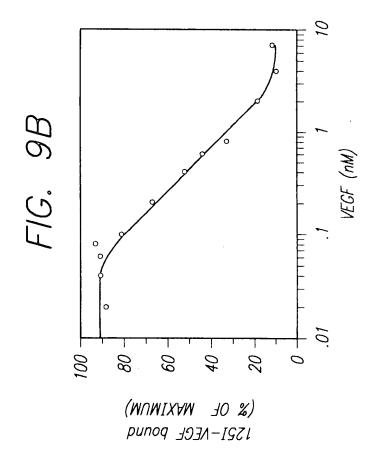
#### MEDIATED VASCULOGENESIS AND ANGIOGENESIS Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

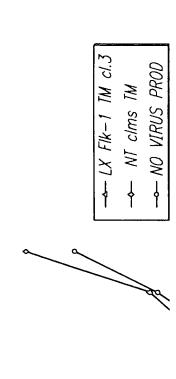




MEDIATED VASCULOGENESIS AND ANGIOGENESIS Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678







400 400 (wm<sup>3</sup>) 40R -VOL (mm<sup>3</sup>) 500 1500 1000

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## FIG. 11-1

CTG																															/5
CGC																															150
GAC	GGA	(GA	AG	GAG	TCT	GTG	icc.	TGA	GA	ΑA	CTG	GG	CT	CT	GTG	icc	CAC	GG(	GC	GAG	iG I	IGC	AG						_		225
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TGC	TΛC	:СТ	ст	ՐԸՐ	ፐሮፐ	CTC	CT.	rrt	የ	'CT	CGA	GΔ	ՐՐ	<u></u> የቤ	ΔGC	ጉርር	٠r.	ררז	GT.	GGO	ודו	rra	ΆC	TGG	irg.	TT	TTC	.ፐር	CAT	۲ſ	300
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TCAA	TG	ΔΤ	GΔ	1 A C	СΤΔ	ΤΓΔ	GTO	`ΤΔ	TC.	ΔΤΩ	TA	۲Δ٦	ΓΔ(	;T1	rgt	GGT	T (	AT:	GG	ΔΤΑ	TΑ	GG	ATI	ГТΑ	TGA	TG	TGA	TT(	CTG	iΑ	900
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GCCC	CC	CG	CA <sup>-</sup>	rga.	AAT	TGA	GCT	'ΑΤ	CT(	GCO	CGG	AG/	۱AA	٩A	ACT	TGT	СТ	TA	AA	TTG	ΤA	CA	GC(	GAG.	AAC	AG	٩GC	TC	٩AT	G	975
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ΔΔΤΔ	CA	۲r	TG"	rg T	ልፍር	STC	CAG	TG	GAO	ርርር	ATO	GAI	r C #	AΑ	AG.	ΑΑΑ	TΑ	GA	AC.	ATT	TG	TC	CG <i>A</i>	GT.	TCA	CAC	CAA.	AG(	СТ	Т	1200
Υ																															
TTAT	TG	СТ	TTO	GG.	TAG	rgg	GAT	GA	٩A٦	тст	TT(	GG 1	G(	SΛA	\GC	CAC	AG	TG	GG(	CAG	TC	AΑ	GTC	:CG/	AAT	CCC	TG:	TGA	۱AG	T	1275
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- 1	C		v	D	٨	D	n	T	L	/	1.1	v	Г	)	M	C	D		D	T	F		C	N	V	T	М	1	i	V	

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## FIG. 11-2

ſΤ	GGC G	GA <sup>-</sup>	TGA.	ACT( L	CAC(	CAT(	CAT( M	GGA <i>F</i> E	AGT0 V	GAC T	TGA. E	AAG R	AGA D	TGC/ A	AGG/ G	NAA(	TA( Y	CAC( T	GGT( V	CAT(	CCT L	CAC(	CAAC N	CCCA P I	1425
П	TC <i>P</i> S	AT( M	GGA E	GAA/ K	Q Q	GAG( S	CCA( H	CATO M	GT( V	CTC S	TCT L	GGT V	TGT V	GAA` N	TGT( V	CCC <i>P</i>	ACC( P	CCA( Q	GAT(	CGG <sup>*</sup>	TGA E	GAA. K	AGCC A	CTTGA L I	1500
rc	TCG S	SCC.	TAT M	GGA <sup>-</sup> D	TTC( S	CTA Y	CCA( Q	GTA1 Y	rgg( G	GAC T	CAT M	GCA Q	GAC T	ATT( L	GAC/ T	ATG( C	CAC <i>i</i> T	AGT( V	CTA( Y	CGC( A	CAA N	CCC <sup>°</sup>	TCC( P	CTGC L H	1575
40	CA( H	I .	CCA Q	GTG( W	GTA( Y	CTG W	GCA( Q	GCT <i>I</i> L	AGA <i>I</i> E	AGA E	AGC A	CTG C	CTC S	CTA Y	CAG/ R	P ACC(	GGG(	CCA/ Q	AAC, T	AAG( S	CCC P	GTA Y	TGC1 A	TGTA C K	1650
Q <i>F</i>	GA <i>F</i> E	ATG( W	GAG R	ACA( H	CGT( V	GGA E	GGA <sup>*</sup> D	TTT( F	CCA( Q	GGG G	GGG G	AAA N	CAA K	GAT I	CGA/ E	AGT( V	CAC(	CAA/ K	AAA N	CCA. Q	ATA Y	TGC A	CCT( L	ATTG I E	1725
	G	K	N	K	T	٧	S	T	L	٧	I	Q	Α	Α	N	٧	S	Α	L	Y	K	.с	Ł	A 1	1800
	N	K	Α	G	R	G	Ε	R	٧	I	S	F	Н	٧	I	R	G	Р	E	Ι	T	٧	Q	РА	
	Α	Q	Р	T	Ε	Q	Ε	S	٧	S	L	L	С	T	Α	D	R	N	T	F	E	N	L	l W	
	Υ	K	L	G	S	Q	Α	T	S	٧	Н	М	G	E	S	L	T	Р	٧	С	K	N	L	υA	
	L	W	K	L	N	G	Τ	М	F	S	N	S	T	N	D	I	L	Ι	٧	Α	ł	Q	N	A 5	
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T	CAT I	TGT V	CC1 L	racg R	GAC T	CGC V	TAA K	AGCG R	iggc A	CA/ N	ATG/ E	AAG( G	GG <i>F</i> E	AACT L	GAA K	GAC T	AGG G	Υ	L	\$ S	IAI. I	161 V	M	D F	2625

nventor(s): Axel ULLRICH et Appl. No.: 09/766,678

## FIG. 11-3

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CAGA <sup>-</sup> D	TGA/ E				GGA D	TGA( E	GCG( R	CTGT C	GA/ E	ACG( R	CTT( L	GCC P	TTA <sup>-</sup> Y	rgat D	rgc( A	CAG( S	CAA( K	STG0 W	GGA <i>F</i> E	\TT( F	CCC( P	CAGO R	GAC( D F	2	2700
GGCT(	GAAA K	ACT <i>i</i> L	AGG/ G	4AA, K	ACC P	TCT L	TGG( G	CCGC R	GGT	rgc( A	CTT( F	CGG G	CCA/ Q	AGT( V	GAT1 I	rga( E	GGC/ A	AGA( D	CGC1 A	ΓΤΤ΄ F	TGG/ G	ITA <i>P</i>	GAC/ D I	A 2	2775
AGAC. T	AGC(	GAC T	TTG( C	CAA. K	AAC. T	AGT. V	AGC(	CGTC V	CAA( K	GAT( M	GTT(	GAA. K	AGA/ E	AGG <i>I</i> G	AGC <i>I</i> A	AAC. T	ACA( H	CAG( S	CGA( E	GCA H	TCG/ R	AGC( A	CTC/ L /	4 2 4	2850
TGTC S	TGA,								GG	TCA H	CCA H	TCT L	CAA N	TGT( V	GGT( V	GAA N	CCT( L	CCT/ L	AGG( G	CGC A	CTG( C	CAC( T	CAAG( K	C 2	2925
CGGG G	AGG G	GCC P	TCT:	CAT M	GGT V	GAT I	TCT(	GCAA Q	ATT( F	CTC S	GAA K	GTT F	TGG. G	AAA( N	CCT/ L	ATC S	AAC T	TTA( Y	CTT/ L	ACG R	GGG G	CAA( K	AGA. R	A : N	3000
ATGA E	ATT F	TGT V	TCC P	CTA Y	TAA K	GAG S	CAA. K	AGG( G	GGC. A	ACG R	CTT F	CCG R	CCA Q	GGG(	CAA( K	GGA D	CTA Y	CGT <sup>.</sup> V	TGG( G	GGA E	GCT L	CTC( S	CGTG V	G : D	3075
ATCT L	GAA K	AAG R	ACG R	CTT L	GGA D	CAG S	CAT I	CAC(	CAG S	CAG S	CCA Q	GAG S	CTC S	TGC A	CAG S	CTC S	AGG G	CTT F	TGT V	TGA E	GGA E	GAA/ K	ATCG S	C : L	3150
TCAG S	TGA D	TGT V	AGA E	GGA E	AGA E	AGA E	AGC A	TTC` S	TGA E	AGA E	ACT L	GTA Y	CAA K	GGA D	CTT F	CCT L	GAC T	CTT L	GGA E	GCA H	TCT L	CAT(	CTGT C	T : Y	3225
ACAG S	CTT F	CCA Q	AGT V	GGC A	TAA K	GGG G	CAT M	GGA E	GTT F	CTT L	GGC A	ATC S	AAG R	GAA K	GTG C	TAT I	CCA H	CAG R	GGA D	CCT L	GGC A	AGC.	ACGA R	A N	3300
ACAT I	TCT L	CCT L	ATC S	GGA E	GAA K	GAA N	TGT V	GGT V	TAA K	GAT I	CTG C	TG <i>A</i> D	CTT F	CGG G	CTT L	GGC A	CCG R	GGA D	CAT I	TTA Y	TAA K	AGA D	CCCG P	G D	3375
	TGT V	CAG R	IAAA K	AGG G	AG <i>A</i> D	TGC A	CCG R	ACT L	CCC P	TTT L	GAA K	NGT(	GAT M	GGC A	CCC P	GGA E	AAAC T	CAT I	TTT F	TGA D	CAG R	AGT V	ATAC Y	A T	3450
CAA7	TCA Q	GA0 S	GCG <i>P</i> D	ATG1 V	GT0 W	GT( S	TTT F	CGG G	TGT V	GT1 L	rgc1 L	rct( W	GGGA E	AAT I	ATT F	TT( S	CTT L	AGG G	TGC A	CTC S	CCC P	ATA Y	CCCT P	G G	3525
GGG <sup>T</sup>	ΓCΑ <i>F</i> Κ	GA <sup>-</sup>	rtg <i>i</i> D	ATG/ E	AAG/ E	AAT F	C C	STAG R	GAG R	GAT <sup>-</sup>	rga <i>i</i> K	AAG/ E	AAG( G	SAAC T	TAG R	AA? M	rgce R	GGC A	TCC P	TG <i>I</i> D	ACT <i>A</i> Y	CAC T	TAC(	C P	3600
CAG	AAA <sup>-</sup> M	TGT. Y	ACC/ Q	AGA T	CCA M	TGC L	TGG/ D	ACT6 C	CT( W	GGC. H	ATG. E	AGG D	ACC( P	CCAA N	ACCA Q	AGA( R	GAC( P	CCT( S	CGTT F	TTT S	CAG/ E	AGT1 L	GGT(	GG E	3675
AGC.	ATT L	TGG G	GAA. N	ACC L	TCC L	TGC Q	AAG( A	CAAA N	ATG! A	CGC Q	AGC Q	AGG D	ATG G	GCA/ K	AAG/ D	ACT. Y	ATA I	TTG <sup>-</sup> V	TTC <sup>-</sup> L	TTC P	CAA <sup>.</sup> M	TGT( S	CAGA( E	GA T	3750
CAC L	TGA S	GCA M	TGG. E	AAG E	AGG D	ATT S	CTG G	GACT L	rct S	CCC L	T&C P	CTA T	CCT S	CAC( P	CTG <sup>*</sup>	TTT S	CCT C	GTA <sup>-</sup> M	TGG/ E	AGG E	AAG/ E	AGG <i>I</i> E	AGT( V	GT C	3825
GCG D	ACC P	CCA K	AAT F	TCC H	ATT Y	ATG D	ACA.	ACA( T	CAG A	CAG G	GAA I	TCA S	GTC H	ATT <i>i</i> Y	ATC L	TCC Q	AGA. N	ACA( S	GTA/ K	AGC R	GAA. K	AGA( S	GCCG R	GC P	3900

### MEDIATED VASCULOGENESIS AND ANGIOGENESIS

Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

## FIG. 11-4

CAGT(		TGT. V	ΑΑΑ <i>ι</i> Κ	AAC, T	ATT F	TGA/	AGA D	TAT I	CCC.	ATT L	GGA E	GGA. E	ACC. P	AGA E	AGT V	AAA K	AGT(	GAT I	CCC. P	AGA D	TGA(	CAG S	CCA Q	GA T	3975
CAGA(	CAG <sup>*</sup> S	TGG G	GAT(	GGT V	CCT L	TGC. A	ATC. S	AGA E	AGA E	GCT L	GAA K	AAC T	TCT L	GGA E	AGA D	CAG R	GAA N	CAA K	ATT L	ATC S	TCC. P	ATC S	TTT F	TG G	4050
GTGG	AAT( M	GAT M	GCC P	CAG S	TAA K	AAG S	CAG R	GGA E	GTC S	TGT V	GGC A	CTC S	GGA E	AGG G	CTC S	CAA N	CCA Q	GAC T	CAG S	TGG G	CTA Y	CCA Q	GTC S	TG G	4125
GGTA Y	TCA H	CTC S	AGA D	TGA D	CAC T	AGA D	CAC T	CAC T	CGT V	GTA Y		CAG S	CGA D	CGA E	GGC A	AGG G	ACT L	TTT L	AAA K	GAT M	GGT V	GGA D	TGC A	TG A	4200
CAGT V	TCA H	CGC A	TGA D	CTC S	AGG G	GAC T	CAC T	ACT L	GAG S	CTC S	CACC P	TCC P	TGT V	TTA	AAT	GGA	AGT	GGT	ССТ	GTC	CCG	GCT	CCG	CC	4275
CCCA CACA TGCC GTGG TCTG ACCT GCGC GTCA GAGT CCCA TCTA	TTTT CATT TCT TGG AAGGA AGGA ACGT ATCT	GATT GAC CAC AAC GCCC AAC GCCC AAC GCCC ACCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCCC ACCC ACCCC ACCC ACCC ACCC ACCC ACCCC ACCC ACCCC AC	TTTTTCCAACCACACACACACACACACACACACACACAC	CCATTA AGA AGA AGA AGA AGA AGA AGA AGA AGA	TTTTALATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	TEGGTA	AGGGCAACTCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	GAGG NAAG NAAG CAGG CAGG CAAAT NAAAT	GGAC GACTAC GCTT GCTT GGCTA GGCT GGCT GG	CTC TTTC TTG TTGA TTGA TTGA TTGA TTGA TT	CAGA CCAGA CGTCTT CAGCC CAGA CCACA CCAGA CCAGA CCACA CCACA CCACA CCACA CCACA CCACA CCACA CCACA CCACA CCACA CCACA CCACA C	ACTEC TTTC ACAC ACAC TGCA TTGC TCCT TCCT TGCA TTGC TTGC	CAACAACAACAACAACAACAACAACAACAACAACAACAA	NGGA NGGA NGGA NGGA NGGA NGGA NGGA NGGA	ATTI ATTI AGGGT AGCT AGGGGC AGGGGC AGGGGC AGGGGC AGGGGC AGGGGC AGGGGC AGGGGC AGGGGG AGGGG AGGGG AGGGG AGGGG AGGGG AGGG AGGG AGGT AGGG AG	FIGHT FAAA FGTCGAG GGGCTC GGGTAA AAAA GGGTA ACT	AAGTTAAAGATGAAAAAAAAAAAAAAAAAAAAAAAAAA	CAGGOOD AND AND AND AND AND AND AND AND AND AN	ATA GAA CAG GAC GAC ACAC ACAC ACAC ACAC	ATTAA AGTO AGGO AGTO AGTO AGTO AGGO TGGO AGGO	TGT GCA GGAG GGAG GGCT GGCT GGCT GGT GGAG GGAG	GCC GCC GCC GCC GCC GCC GCC GCC GCC GCC	CCTG GCA CTGT AGGA CCCC AGGA FGGA	ACT ACC ACT AGC AGC AGC AGC ACC	4350 4425 4500 4575 4650 4725 4800 4875 4950 5025 5100 5175 5250 5325 5393

ANGIOGENESIS Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678

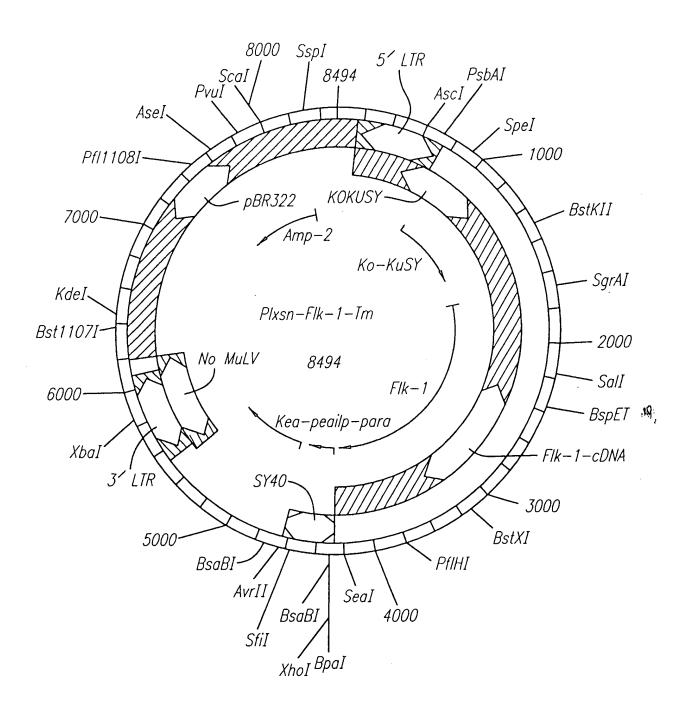
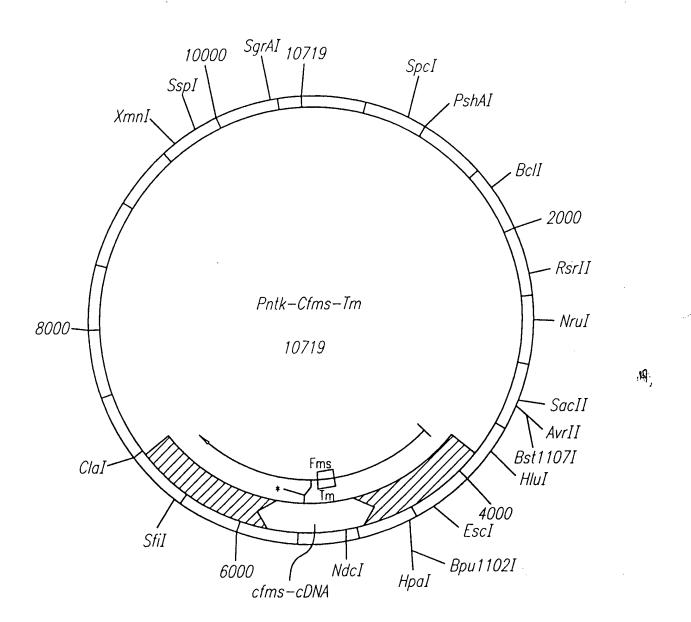


FIG. 12A

#### **ANGIOGENESIS**

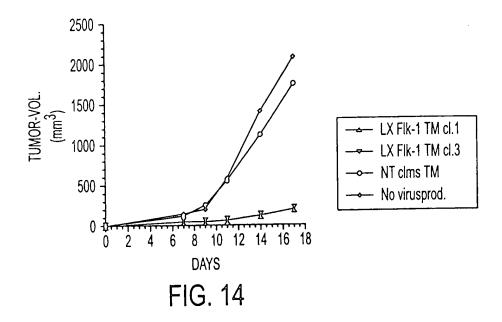
Inventor(s): Axel ULLRICH et al.

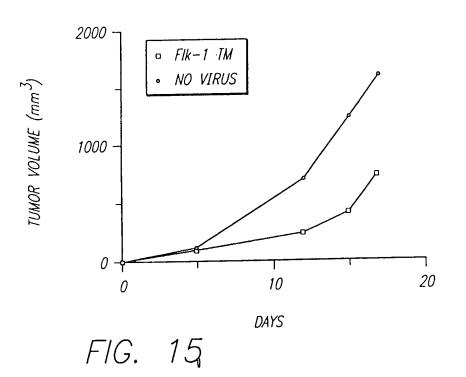


FĮG. 12B

### MEDIATER VASCULLUSENESIS AND ANGIOGENESIS

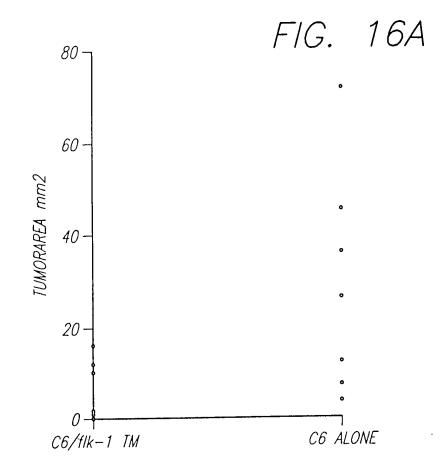
Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678





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ANGIUGENESIS Inventor(s): Axel ULLRICH et al. Appl. No.: 09/766,678



W,

